



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Gordon J. Freeman, Vassiliki A. Boussiotis, and Lee M. Nadler

Serial No.: 08/446,200

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For: *Methods for Selectively Modulating A TH2-Type Response Within a Population of Activated CD4<sup>+</sup> T Cells*

Attorney Docket No.: RPI-033

Group Art Unit: 1644

Examiner: Rabin, E.

#18  
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5/12/95

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**APPEAL BRIEF**

As set forth in the Notice of Appeal filed on September 29, 1998, and received by the U.S. Patent Office on October 2, 1998, Appellants hereby appeal the final decision of the Examiner in the above-identified application rejecting the subject matter of the pending claims. Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the Examiner's rejection of the claimed subject matter.

**I. REAL PARTY IN INTEREST**

The real party in interest in the above-identified application is Dana Farber Cancer Institute.

**II. RELATED APPEALS AND INTERFERENCES**

No other appeals or interferences are known to Appellants, Appellants' legal representative or the assignees which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**III. STATUS OF CLAIMS**

Claims 1-59 were pending in this application. Claims 5-59 have been canceled without prejudice in the Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116, which is being filed on even date herewith. The amendment and/or cancellation of these claims reduces the number of issues for appeal. It is assumed that the Amendment and Response to Final Office Action will be entered for purpose of appeal and the claims argued herein will reflect this assumption. All of the pending claims are on appeal and are set forth in Appendix A of this Brief.

**IV. STATUS OF THE AMENDMENTS**

An Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 is being filed on even date herewith in response to the final Office Action dated March 31, 1998 (Paper No. 12). A Notice of Appeal was filed separately on September 29, 1998, and received by the U.S. Patent Office on October 2, 1998.

In the Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116, claims 5-59 have been canceled without prejudice.

It is assumed that the Amendment and Response to Final Office Action will be entered for purpose of appeal and the claims argued herein will reflect this assumption.

No other amendments after final have been filed. All other amendments have been entered.

## V. SUMMARY OF THE INVENTION

Appellants' invention pertains to a method for selectively modulating a Th2-type response within a population of activated CD4+ T cells by contacting the population of activated CD4+ T cells with an agent, e.g., a stimulatory form of B7-2 (for example, attached to a solid phase support), which modulates, e.g., an agent which stimulates, a B7-2-induced signal in the population of activated CD4+ T cells, such that the Th2-type response is modulated, as described at, for example, page 3, lines 26-32.

## VI. STATEMENT OF ISSUE PRESENTED FOR REVIEW

Appellants present the following issues for review:

I. Whether claims 1-4 are unpatentable under U.S.C. § 103 as being obvious over Hathcock *et al.* [J. Exp. Med. 180: 631-640 (1994)], in view of Linsley *et al.* [U.S. Patent 5,580,756], Kuchroo *et al.* [Cell 80: 707-718 (March 1995)] and Janeway *et al.* [Cell 76: 275-285 (1994)].

## VII. GROUPING OF CLAIMS

Claim 1 is Appellants' principal claim on appeal. Claim 1 is an independent genus claim drawn to a method for selectively modulating a Th2-type response within a population of activated CD4+ T cells. The method includes contacting the population of activated CD4+ T cells with an agent which modulates a B7-2-induced signal in the population of activated CD4+ T cells, such that the Th2-type response is modulated.

Claims 2-4 depend from claim 1. Claim 2 is directed to a method of claim 1, in which the Th2-type response is induced by contacting the population of activated CD4+ T cells with an agent which stimulates a B7-2-induced signal. Claim 3 is directed to a method of claim 2, in

which the agent which stimulates a B7-2-induced signal in the population of activated CD4+ T cells is a stimulatory form of B7-2. Claim 4 is directed to a method of claim 3, in which the stimulatory form of B7-2 is a form of B7-2 which is attached to a solid phase support.

The rejected claims do not stand or fall together for the reasons set forth below.

## VIII. ARGUMENTS

### Rejection of Claims 1-4 Under 35 U.S.C. § 103(a)

The Examiner has maintained her rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over *Hathcock et al.* [J. Exp. Med. 180: 631-640 (1994)] in view of *Linsley et al.* [U.S. Patent 5,580,756], *Kuchroo et al.* [Cell 80: 707-718 (1995)] and *Janeway et al.* [Cell 76: 275-285 (1994)], for the same reasons as set forth in the previous Office Action. In particular, the Examiner is of the opinion that "one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)." Moreover, the Examiner argues that

the use of soluble receptors was well known in the art at the time of the invention. As evidence has come forth for interactions between membrane bound cell surface receptors and "partner receptors" in the interaction have been identified, the effects of soluble receptors, recombinant soluble receptors, and immobilized recombinant soluble receptors have been established. This pattern has been seen for more than a decade. Therefore, given the state of the art of the time of the invention and the motivation provided by the references, one would have substituted soluble B72-Ig for B72 in modulating an immune response.

With regard to *Kuchroo et al.* the Examiner argues that

*Kuchroo et al.* clearly show on Page 715, Column 1 and Figure 7, as cited by the Examiner in Paper No. 8, "that the simplest interpretation of our data is that B7-1 preferentially acts as a costimulator for the generation of Th1 cells while B7-2 costimulates and induces Th2 cells (see model in Figure 7)." The claim recites "with an agent which stimulates a B7-2 induced signal". This would be

interpreted by those in the art as an agent that acts in place of B7-2 to induce a signal on its partner, the counter-receptor of B7-2. The counter receptors of B7-2 are CD28 and CTLA-4. A stimulatory antibody interacting with the membrane bound B7-2 cell surface receptor would not be considered to be stimulating a B7-2 induced signal. In Figure 7, B7-2 is clearly depicted as interacting with CD28/CTLA-4, *i.e.*, as engaging in a B7-2-induced signal.

Therefore, the Examiner concludes

one of ordinary skill in the art at the time the invention was made would have been motivated to stimulate CD3-activated T cells to differentiate to Th2 cells by activating them with immobilized soluble B7-2. One would have been motivated *to substitute soluble B7-2 for B7 in the teachings of Linsley et al. because of Hathcock's teaching of B7-2 on activated B cells*, Kuchroo's teaching that interaction with B7-2 induces activated T cells to differentiate to become Th2 cells, and Linsley's teaching that immobilized soluble B7 is very effective. One would have been motivated to combine these teachings because signals involved in Th cell differentiation was a problem important in the art as evidenced by the teachings of Kuchroo *et al.* and Janeway *et al.*, for example. Based on the teachings of Linsley *et al.* and Kuchroo *et al.*, for example, one of ordinary skill in the art would have a reasonable expectation of success in modulating the immune response by immobilized, soluble, stimulatory B7-2. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness, since the cited references alone or in combination, fail to teach or suggest the claimed methods, for the following reasons.

To begin with, Appellants respectfully submit that even though they agree with the Examiner that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references", Appellants do need to analyze the references individually to decipher whether the references, in fact, teach that which the Examiner alleges they teach.

A. Hathcock *et al.* fail to teach or suggest different roles for B7-1 and B7-2

The Examiner relies on Hathcock *et al.* for teaching the expression, regulation and function of B7-2, and for teaching that B7-1 and B7-2 are expressed/induced with differing kinetics and play different roles in initiating and maintaining an immune response. In particular, the Examiner contents that,

[H]athcock *et al.* teach that in response to LPS or anti-IgD-dextran, murine B cells express B7-2 earlier and at higher levels than B7-1 and that such quantitative differences in the amount of B7-1 and B7-2 expressed on activated B cells may, profoundly influence their contribution to costimulatory function (Pages 634 and 638, in particular).

First, Appellants submit that Hathcock *et al.* teach the following observations which are set forth in the "Summary" section at page 631: (a) B7-1 and B7-2 can be expressed by multiple cell types, including B cells, T cells, macrophages, and dendritic cells; (b) stimulating B cells with either LPS or anti-IgD-dextran induced expression of both B7-1 and B7-2; (c) blocking of B7-2 costimulatory activity inhibited TCR-dependent T cell proliferation and cytokine production; and (d) expression of B7-1 and of B7-2 can be regulated by a variety of stimuli. Hathcock *et al.* do not teach or suggest ***modulating a Th-2 type response*** in a population of CD4+ T cells by contacting these cells with an agent which modulates a B7-2 induced signal. In fact, there is no teaching in Hathcock *et al.* relating to the Th-1 and Th2 pathways of maturation of CD4+ T cells, nor is there a teaching or suggestion relating to ***the differential role of B7-1 and B7-2 in these pathways***.

Moreover, there is no support for the Examiner's position that since Hathcock *et al.* teach that "quantitative differences" exist in the amount of B7-1 and B7-2 expressed on activated B cells, these differences can "profoundly influence" the contribution of B7-1 and B7-2 to costimulatory function. In contrast, Hathcock *et al.* teach that "the kinetics of peak expression of these two costimulatory molecules was, in fact, ***not different***" (see page 638, first column, first full paragraph). Moreover, Hathcock *et al.* teach that "[i]t is not yet clear whether different

*costimulatory molecules such as B7-1 and B7-2 mediate distinct function in the course of immune responses*" (see page 638, first column, first full paragraph) and that "[a]t the current time, *it is not known whether B7-1 and B7-2 mediate distinct or overlapping costimulatory functions*" (see page 638, second column, first full paragraph). Thus, this reference not only fails to provide support for the Examiner's position, but further fails to provide a motivation for making the claimed invention, as Hathcock *et al.* teach that it was not known that B7-1 and B7-2 mediate different functions.

B. One of ordinary skill in the art would not have been motivated to substitute soluble B7-2 for B7 in view of the teachings of Linsley *et al.*

The Examiner relies on Linsley *et al.* for teaching the use of soluble B7 including fragments and derivatives to stimulate T cells. First, it is the Examiner's position that "one [of ordinary skill in the art] would have been motivated to substitute soluble B7-2 for B7 in the teachings of Linsley *et al.* because of Hathcock's teaching of B7-2 on activated B cells." Appellants respectfully submit that the proposed combination of Hathcock *et al.* and Linsley *et al.* fails to teach or suggest the claimed invention. First, as set forth above, Hathcock *et al.* fails to provide the necessary *motivation* for the ordinarily skilled artisan to substitute soluble B7-2 for B7 in the teachings of Linsley *et al.* because Hathcock *et al.* fails to teach or suggest *different* roles for B7-1 and B7-2 in T cell mediated responses. Given the lack of such a teaching, the ordinarily skilled artisan would not have looked to the teachings of Linsley *et al.* with respect to a soluble B7-Ig fusion molecule to modulate Th2-type responses.

Moreover, Linsley *et al.* does not make up for the deficiencies of Hathcock *et al.* Specifically, Linsley *et al.* *fail to distinguish between the B7-1 and the B7-2 molecules and,* thus, fails to provide the motivation for the ordinarily skilled artisan to modulate *Th2-type responses* by modulating B7-2 induced signals. In addition, there is no teaching or suggestion in Linsley *et al.*, as suggested by the Examiner, that such responses could be modulated by use of an agent which modulates a B7-2 induced signal. Thus, the proposed combination of Hathcock

et al. and Linsley et al. as above, or with any of the other cited references, fails to teach or suggest the claimed invention and fails to provide the necessary motivation to the ordinarily skilled artisan to make the claimed invention.

C. Since Kuchroo et al. teach away from the claimed invention, they fail to make up for the deficiencies in the other cited references

The Examiner relies on Kuchroo *et al.* for teaching that "their data in experiments using anti-B7-1 and anti-B7-2 antibodies are direct evidence that interaction of the costimulatory molecules B7-1 or B7-2 with their counter receptors CD28 and CTLA-4 on T helper precursors (Thp) during antigen presentation leads to polarization of Th responses" and "that the simplest interpretation of their data is that B7-1 preferentially acts as a costimulator for the generation of Th1 cells while B7-2 costimulates and induces Th2 cells (Page 715, Column 1 and Figure 7, in particular)". Furthermore, it is the Examiner's position that Kuchroo *et al.* provide the necessary motivation to the ordinarily skilled artisan to substitute "soluble B7-2 for B7 in the teachings of Linsley et al." because of "Kuchroo's teaching that interaction with B7-2 induces activated T cells to differentiate to become Th2 cells."

Appellants respectfully submit that Kuchroo *et al.* fail to support the above-quoted position of the Examiner. Kuchroo *et al.* teach that CD4 T helper precursor cells mature along two alternative pathways (Th-1 and Th-2) and that these pathways are differentially activated by B7-1 and B7-2. Kuchroo *et al.* focus on the implications of this biological observation, in terms of susceptibility or resistance to a particular disease, but fail to teach or suggest a method for modulating a Th2-type response in a population of CD4+ T cells by contacting these cells with an agent which modulates a B7-2 induced signal. More importantly, Kuchroo *et al.* teach that an anti-B7-2 antibody *enhances the production of INF $\gamma$*  (see page 708, first column, second paragraph), a cytokine known in the art and taught by Appellants to direct CD4+ T cells to differentiate into ***Th1 cells, not Th2 cells***. This cytokine is also secreted by Th1 cells. In contrast, Appellants discovered that Th2 responses can be induced by stimulation of T cells with

B7-2. Thus, in view of the above described teachings of Kuchroo *et al.*, the ordinarily skilled artisan would have concluded that an agent which modulates a B7-2 induced signal in CD4+ T cells, would result in a ***Th1-type response not a Th2-type response***. In view of this conclusion, the ordinarily skilled artisan would not have been motivated to contact a population of activated CD4+ T cells with an agent which modulates a B7-2-induced signal in the population of activated CD4+ T cells to thereby modulate a ***Th2-type response***. Given a lack of motivation to make the claimed invention in Kuchroo *et al.* or any of the cited references, the Examiner has failed to establish a *prima facie* case of obviousness.

D. Janeway *et al.* Fail to Make up for the Deficiencies in the Primary and Secondary References

Finally, Janeway *et al.* is relied on by the Examiner, for teaching that "one of the most crucial events in the differentiation of naive CD4 T cells that respond to a ligand presented together with a costimulator is the decision whether to become a helper CD4 T cell (Th2) ... or an inflammatory CD4 T cell (Th1)" and for teaching that "if the biochemical nature of differential signaling pathways are known, pharmacological agents can be developed capable of diverting T cell responses". Janeway *et al.* is further relied on by the Examiner as providing the motivation to combine the teachings of the cited references "because signals involved in Th cell differentiation was a problem important in the art as evidenced by the teachings of ... Janeway *et al.*"

Appellants respectfully submit that Janeway *et al.* fail to make up for the above-described deficiencies of the primary and secondary references for the following reasons. First, Janeway *et al.* is a review article describing adaptive immune responses of naive lymphocytes. Although, Janeway *et al.* teach the differentiation of naive CD4 T cells into either Th2 or Th1 cells, Janeway *et al.* fail to teach or suggest a role for the B7-1 and B7-2 molecules in this differentiation process. Moreover, Janeway *et al.* fail to teach or suggest agents which modulate a B7-2 induced signal to thereby modulate a Th-2 type response in a population of CD4+ T cells.

Accordingly, Janeway *et al.* fail to provide the necessary motivation to combine the teachings of the cited references as proposed by the Examiner, as Janeway *et al.* fail to teach or suggest a role for B7-2 in the differentiation of naive CD4+ T cells into either Th1 or Th2 cells.

In view of the above, Appellants respectfully submit that none of the cited references, alone or in combination, teach or suggest a method for modulating a Th2-type response in a population of CD4+ T cells by contacting these cells with an agent which modulates a B7-2 induced signal. Moreover, in view of the above, the Examiner has failed to provide evidence that the ordinarily skilled artisan would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention.

E. The Teachings Of The Cited References Relied Upon By The Examiner To Combine The References Are Legally Insufficient To Provide The Requisite Motivation

Moreover, Appellants respectfully submit that the Examiner has failed to point to any teaching in the cited references which would impel one of ordinary skill in the art to make the claimed invention. The prior art must suggest "to those of ordinary skill in the art that they **should** make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success **must be founded in the prior art, not in the applicant's disclosure** (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

It is Appellants' position that the teachings of the cited references relied upon by the Examiner to combine the references are legally insufficient to provide the requisite motivation. With regard to the necessary legal standard, Appellants refer the Examiner to *Arkie Lures v. Larew Tackle*, 119 F.3d 953, (Fed. Cir. 1997). In Arkie Lures, the Larew invention was directed to a "salt-impregnated fishing lure." In that case, the CAFC overturned the district court's finding of obviousness. The CAFC agreed that "[t]he use of salty bait to catch fish was known,[and] plastisol lures were known." *Id* at page 956. However, the CAFC found that although the literature on "fishing lures is apparently quite extensive, but despite the long use of

salty lures and plastic lures, no reference was cited that showed or suggested this combination."

The CAFC continued that "[t]he evidence showed the complexity of the plastic fishing lure art. Those in the field of the invention viewed Larew's invention not as a simple concept of adding salty taste to a known lure, but as a complex combination requiring experience of fishing and fishing lures and the technology of plastics." Id at page 957.

The court further stated that:

No prior art showed or suggested the combination of a plastisol lure with salt, although the prior art was extensive as to the separate elements, and suggested including organic attractants in plastic lures. . . . The question is not whether salt "could be used," as the district court concluded, but whether it was obvious to do so in light of all the relevant factors. . . . *It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements.* Indeed, the years of use of salty bait and of plastic lures, without combining their properties, weighs on the side of unobviousness of the combination (emphasis added).

*Id* at pages 957 and 958.

Similar to the situation in the Arkie Lures case, it is Appellants' position that despite the fact that the prior art contained separate elements of the present invention, these individual teachings are insufficient to establish the obviousness of the claimed invention absent some teaching or suggestion in the art to combine and modify the teachings of those references to arrive at the claimed invention. It is Appellants' position that the motivation relied upon by the Examiner, which is not based on explicit suggestions within the cited references, but rather on what the Examiner argues that one of ordinary skill in the art would have known, is legally insufficient to establish the requisite suggestion to combine references.

Additional support of the position that the claimed invention is unobvious is found in *In re Vaeck (In re Vaeck 947 F.2d 488. (Fed. Cir. 1991))* where the CAFC upheld the nonobviousness rejections of a biotechnology invention. In *Vaeck* the invention was drawn to "a

chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing the *Bacillus* gene in a host cyanobacterium, so as to produce the desired insecticidal protein (footnote omitted)." *Id* at page 490. The prior art (a total of eleven references) was applied in various combinations against the claims. The primary reference (Dzelzkalns) taught the expression of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT) in cyanobacteria. The secondary references taught, *inter alia*, "expression of genes encoding certain *Bacillus* insecticidal proteins" in other host cells; "the initiation specificities *in vitro* of DNA-dependent RNA polymerases purified from two different species of cyanobacteria (footnote omitted); and "a host-vector systems for gene cloning in the cyanobacterium." *Id* at page 491. The Examiner's position was that:

it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes [which had been expressed in heterologous hosts in the teachings of the prior art] for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The Examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the expression of heterologous genes.

*Id* at page 492. The CAFC disagreed with the Examiner's position and found that the teachings of the prior art cited in *Vaeck* were not sufficient to support the interchangeability of bacteria and cyanobacteria as host organisms for the expression of heterologous insecticidal proteins. The court stated that "there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria." *Id* at page 493. The court further stated that

while the prior art disclosed "expression of *Bacillus* genes encoding insecticidal proteins in certain transformed bacterial hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts. . . . [w]hile it is true that bacteria and cyanobacteria are now both classified as prokaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends. *Id* at pages 493 and 494.

The CAFC contrasted its findings in *In re Vaeck* with those in *In re O'Farrell* stating "[i]n contrast with the situation in *O'Farrell*, the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art." In *O'Farrell* the invention was directed to a "method for producing a predetermined protein in a stable form in a transformed host species of bacteria." *In re O'Farrell* 853 F.2d 894. 1988. 7 U.S.P.Q. 2d (BNA) 1673. The prior art (Polisky) taught a previous attempt to "control the expression of cloned heterologous genes inserted into bacteria." *Id* at page 899. The prior art differed from the claim at issue, however, because it taught a method of expressing "a segment of DNA from a frog that coded for ribosomal RNA," which is normally not translated into protein. Although ribosomal RNA is not normally translated into protein, the court found that in the prior art publication by Polisky the authors were "obviously interested in using their approach to make heterologous proteins in bacteria." *Id* at page 900. The CAFC referred to the Polisky paper which stated:

In fact, we have recently observed that induced cultures of pBGP123 contain elevated levels of [beta]-galactosidase of higher subunit molecular weight than wild-type enzyme (P. O'Farrell, unpublished experiments). We believe this increase results from translation of Xenopus [frog] RNA sequences covalently linked to [messenger] RNA for [beta]-galactosidase, resulting in a fused polypeptide.

*Id* at page 900 (quoting from Polisky et al. at page 4904). The court stated that "[t]he authors of the Polisky paper **explicitly pointed out** that if one were to insert a heterologous gene coding for a protein into their plasmid, it should produce a 'fused protein' consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene, joined by a peptide bond

into a single continuous polypeptide chain." *Id* at page 901. The court also referred to a passage in the Poliskiy reference, where the authors stated that "[i]f an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide." *Id* at page 901 (quoting from Poliskiy et al.). The court upheld the PTO decision that the claims in *O'Farrell* were obvious over Poliskiy because:

*virtually everything in the claims was present in the prior art. . . .*

The main difference is that in Poliskiy the heterologous gene was a gene for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. . . . Nevertheless, Poliskiy mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Poliskiy further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, 'a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide.' ***Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.*** (emphasis added).

*Id* at 901.

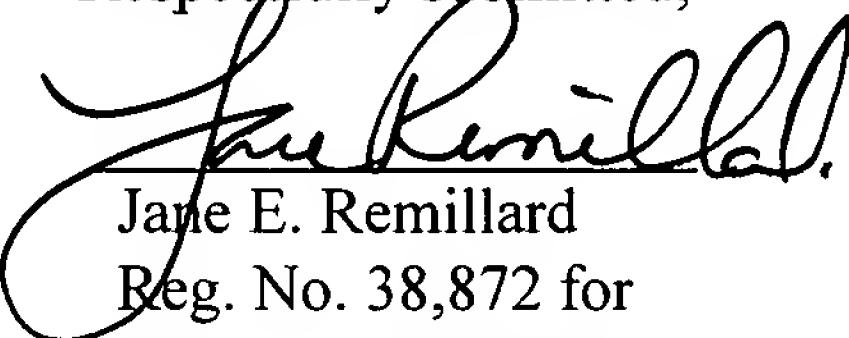
It is Appellants' position that, as in *In re Vaeck*, there is no teaching, either explicit nor implicit, in any of the references cited by the Examiner which would have impelled one of ordinary skill in the art to make the instantly claimed invention. The art cited by the Examiner is directed to different aspects of the claimed invention. Hathcock *et al.* teach that B7-1 and B7-2 can be expressed by multiple cell types; that stimulating B cells with either LPS or anti-IgD-dextran induced expression of both B7-1 and B7-2; that blocking of B7-2 costimulatory activity inhibited TCR-dependent T cell proliferation and cytokine production; and that expression of B7-1 and of B7-2 can be regulated by a variety of stimuli. Linsley *et al.* identify B7 as a ligand recognized by the CD28 receptor and disclose a B7Ig fusion protein. Kuchroo *et al.* teach that CD4 T helper precursor cells mature along two alternative pathways (Th-1 and Th-2) and that these pathways are differentially activated by B7-1 and B7-2, but based on the teachings of

Kuchroo *et al.* the ordinarily skilled artisan would have concluded that an agent which modulates a B7-2 induced signal in CD4+ T cells, would result in a ***Th1-type response not a Th2-type response***. Finally, Janeway *et al.* teach the differentiation of naive CD4 T cells into either Th2 or Th1 cells, but fail to teach or suggest a role for the B7-1 and B7-2 molecules in this differentiation process. Given the standard for obviousness set forth by the CAFC, it is Appellants' position that the Examiner has improperly relied on hindsight obtained from Appellants' invention in making the combination of references cited.

## VII. CONCLUSION

Appellants submit that pending claims 1-4 are patentable and it is respectfully requested that the Board reverse the final rejection of the subject matter of these claims for the reasons given above.

Respectfully submitted,



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APPENDIX A

1. A method for selectively modulating a Th2-type response within a population of activated CD4+ T cells, comprising contacting the population of activated CD4+ T cells with an agent which modulates a B7-2-induced signal in the population of activated CD4+ T cells, such that the Th2-type response is modulated.
2. The method of claim 1, wherein the Th2-type response is induced by contacting the population of activated CD4+ T cells with an agent which stimulates a B7-2-induced signal.
3. The method of claim 2, wherein the agent which stimulates a B7-2-induced signal in the population of activated CD4+ T cells is a stimulatory form of B7-2.
4. The method of claim 3, wherein the stimulatory form of B7-2 is a form of B7-2 which is attached to a solid phase support.